IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: **YANAGISAWA, Katsuhiko, et al.**

Serial No.: **10/768,193**

Group Art Unit: **1649**

Filed: **February 2, 2004**

Examiner: **Kimberly A. Ballard**

P.T.O. Confirmation No.: 3691

For: **ANTIBODY RECOGNIZING GM1 GANGLIOSIDE-BOUND AMYLOID (BETA)-PROTEIN AND DNA ENCODING THE ANTIBODY**

DECLARATION UNDER 37 CFR 1.132(b)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Katsuhiko Yanagisawa, a citizen of Japan, hereby declare and state:

1. I am a named inventor on U.S. patent application Serial No. 10/768,193, "Antibody recognizing GM1 ganglioside-bound amyloid β-protein and DNA encoding the antibody", which in the following I refer to as the "subject application".

2. Furthermore, I am the named senior author on Hayashi et al., The Journal of Neuroscience 24, (2004), 4894-4902 ("D1") and I am the leading author of Yanagisawa et al., FEES LETT. 420 (1997), 43-46 ("D2") and Yanagisawa et al., Neurobiol. Aging 19 (1998), 65-67 ("D3").

3. I am familiar with the present application as well as with the mentioned references. Furthermore, I have been made familiar with the file history of the subject application including an Office Action issued by the United States Patent Office on February 23, 2007.

4. I am additionally advised and therefore believe that the Examiner has issued two rejections in the February 23, 2007 Office Action which, in asserting that the claims allegedly lack novelty and/or inventive step, potentially raises the following questions:

(a) Following the instructions in D2, would the person skilled in the art be enabled to arrive at the antibody described therein or antibodies with similar advantageous properties?

(b) Was it possible that third parties could have access to the antibody described in D2 because of the publication?

(c) Were there any restrictions in the distribution of samples of the claimed antibody to other scientists?

In the following, I would like to comment on the above issues.

5. In this declaration, I use the commonly abbreviated term for "GM1 ganglioside-bound amyloid β-protein (Aβ), "GM1/Aβ". Aβ is a proteolytic cleavage product of β-amyloid precursor protein (βAPP) and a portion of Aβ molecules tightly binds to GM1 ganglioside in the brains of subjects in the early stages of Alzheimer's disease (AD).

6. I understand that the claims in the subject application involve recombinant anti-GM1/Aβ-antibodies which are characterized by their biological activity of inhibiting the formation of amyloid fibrils and their binding specificity, i.e. recognition of Aβ bound to lipid vesicles containing GM1 ganglioside but not soluble Aβ or GM1 ganglioside. In particular, the claims of the subject application are related to an antibody which has been established in my laboratory, and which has been designated 4396, i.e. the 4396 antibody.

Please note that the antibody described in D2 and used to perform the experiments described therein is an IgM class, while the antibody disclosed in the present application is a recombinant IgG class antibody, i.e. antibody 4396C, also referred to hereinafter as the subject antibody. Compared to the original 4396 antibody, the subject antibody has the advantage of showing a lower activity of non-specific absorption and being hard to aggregate, which makes the claimed antibody much more suitable for diagnostic and pharmaceutical applications. Furthermore, please also note that, in D2, we were not able to conclude that 4396 antibody specifically recognizes GM1/Aβ.

7. The hybridoma producing the 4396 antibody has been established by myself in 1996 and used for experiments in my laboratory, e.g. for the experiments referred to in D2. However, I have never made the hybridoma available to others except described below and even not to my colleagues co-authoring D2, to whom only samples of the 4396 antibody itself were provided just sufficient to perform the intended experiments that have been approved by

me beforehand. Needless to say that my colleagues were obliged to use the 4396 antibody for the purpose of the experiments agreed upon only.

8. Furthermore, I have described the method for preparation of the subject antibody and the hybridoma in D2 in general terms; however, the screening for positive clones were extremely difficult. Thus, it is hardly believed that 4396 antibody can be easily generated by any other party. I was really lucky in identification and isolation of the initial hybridoma producing the so-to-say precursor antibody 4396 which gave rise to the claimed antibody. Importantly, in D2, this antibody was merely used as a means for characterizing the immunoreactivity of Aβ bound to membrane lipids.

9. More importantly, a sample of the hybridoma cell line producing the 4396 antibody and its nucleotide and amino acid sequence have never been distributed at all, only except sending the hybridoma or the antibody to agencies to entrust technical support, including multiplication of the hybridoma, purification of 4396 antibody and preparation the antibody-bound column and generation of the subject antibodyl! (4396C). Although we sent 4396 antibody to scientists including my collaborators in D2, it would not have been possible to produce the 4396 antibody, let alone the subject antibody. Rather, after performing the intended experiment, the practitioner would have run out of the antibody material.

Accordingly, before the effective filing date of the subject application, the 4396 antibody described in document D2 and the subject antibody were not available to the public.

10. On the basis of the results of experiments using the subject antibody 4396C, I recognized the advantageous and superior properties of the subject antibody compared to other anti-Aβ antibodies published before. It was therefore that I decided to elucidate the nucleotide and amino acid sequence of the subject antibody, i.e. its variable domain and to file a patent application, i.e. the subject application.

11. From the February 23, 2007 Office Action I understand that the Examiner possibly believes that in view of the mentioning of the 4396 antibody in document D2 it could have been made available to the public or that this one could have been arrived at by standard techniques.

I, as senior author of document D2 as well as co-inventor on the subject application, respectfully disagree with the Examiner.

12. In fact, as the Examiner will note, paragraphs 2.2 and 2.3 of "Materials and Methods" of D2 do not indicate any specific information as to how to arrive at the 4396 antibody and the hybridoma producing it, respectively. In this context, I would like to emphasize that the use of membrane fractions referred to by the Examiner is by no means sufficient to arrive at the 4396 antibody or an equivalent antibody. Please note that the previous antibodies BC05 and BAN052 recognized such membrane fractions as well; see Figure 2 and paragraph 3.2 at page 45 of D2. In fact, from reviewing the method of generating the hybridoma producing the 4396 antibody, I and my colleagues as well have no explanation as to the unique properties of the 4396 antibody compared to those of BC05 and BAN052, for instance that the 4396 antibody does not immunoprecipitate synthetic Aβ and exhibits greater binding affinity for Aβ bound to phosphatidylinositol (PI); see also the discussion in D2 at page 46.

Thus, I believe that it was just a stroke of luck to select the hybridoma producing the 4396 antibody and I firmly believe that based on the information provided in D2 only, it would hardly be possible to arrive at such hybridoma again or at an hybridoma producing an antibody with similar properties, let alone the same properties.

13. In summary, in view of the discussion herein above, I very respectfully assert that D2, either individually or in any combination with other prior art documents, is not sufficient for providing the 4396 antibody. And it is also very respectfully asserted that inventive effort was required to arrive at the subject antibody.

14. Moreover, the present invention provides surprising and unexpected results. As has been shown for the subject antibody, in the present application, it is capable of inhibiting the formation of amyloid fibrils in the presence of GM1-containing liposomes; see Example 4 and Figure 6 of the present application. These results have also been published in D1 and provide one step further in the understanding of the mechanism underlying the onset of Alzheimer's disease and a target for therapeutic intervention. Moreover, my research group could recently show that the peripheral administration of Fab fragments of the subject antibody into transgenic mice expressing a mutant amyloid precursor protein gene markedly suppressed AP deposition in the brain. This further supports the therapeutic value of the antibody of the present invention.

15. For the above reasons it is very respectfully submitted that D2, either individually or in combination with D3 or any other prior art, is not sufficient for providing the antibody claimed in the subject application, i.e. that D2, either individually or in any combination, does not destroy the novelty or the inventive step of the instant invention. Inventive effort was required to achieve the instant invention. It is also very respectfully submitted that as an additional evidence of the patentability of the instant invention, the subject antibody of the instant invention achieve surprising and unexpected results. Accordingly, it is very respectfully submitted that the instant invention is patentable.

16. The undersigned declares that all statements made herein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed this 16th day of May, 2007

Katsuhiko Yanagisawa